Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study

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Summary

Background Trastuzumab deruxtecan (DS-8201a) is a novel HER2-targeted antibody–drug conjugate with a humanised anti-HER2 antibody, cleavable peptide-based linker, and topoisomerase I inhibitor payload. A phase 1, non-randomised, open-label, multiple-dose study was done to assess the safety, tolerability, and activity of trastuzumab deruxtecan in HER2-expressing advanced solid tumours. The dose escalation (part 1) has previously been reported and the recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg were established. In this Article, we report the safety and preliminary activity results from this phase 1 trial in all patients with HER2-positive gastric or gastro-oesophageal junction cancer who received trastuzumab deruxtecan at the recommended doses for expansion.

Methods This was an open-label, dose-escalation and dose-expansion phase 1 trial done at eight hospitals and clinics in the USA and six in Japan. Eligible patients were at least 18 years old in the USA and at least 20 years old in Japan and had advanced solid tumours (regardless of HER2 expression in dose escalation or HER2 expression or mutation in dose expansion). The recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg trastuzumab deruxtecan were administered intravenously to patients once every 3 weeks until withdrawal of consent, unacceptable toxicity, or progressive disease. In this Article, all patients with HER2-positive gastric or gastro-oesophageal junction cancer with previous trastuzumab treatment who received trastuzumab deruxtecan were analysed together. The primary endpoints of the study were safety and preliminary activity (proportion of patients who achieved an objective response as assessed by the investigators). The activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion, and for whom both baseline and post-treatment activity data were available. The safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. Enrolment for patients with gastric or gastro-oesophageal junction cancer has completed. This trial is registered at ClinicalTrials.gov, number NCT02564900, and ClinicalTrials.jp, number JapicCTI-152978.

Findings Between Aug 28, 2015, and Aug 10, 2018, 44 patients with HER2-positive gastric or gastro-oesophageal junction cancer received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. All patients had at least one treatment-emergent adverse event. The most frequent grade 3 or worse treatment-emergent adverse events included anaemia (13 [30%]) and decreases in neutrophil (nine [20%]), platelet (eight [18%]), and white blood cell (seven [16%]) counts. Serious treatment-emergent adverse events occurred in 11 (25%) patients. There were four pneumonitis cases (three grade 2 and one grade 3). There were no drug-related deaths due to treatment-emergent adverse events. 19 (43·2%; 95% CI 28·3–59·0) of 44 patients had a confirmed objective response.

Interpretation Trastuzumab deruxtecan had a manageable safety profile and showed preliminary activity in heavily pretreated patients with HER2-positive gastric or gastro-oesophageal junction cancer. These results support further investigation of trastuzumab deruxtecan for HER2-positive gastric or gastro-oesophageal junction cancer post-trastuzumab.

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Introduction

Gastric cancer is the third leading cause of cancer death worldwide.[1] In 2012, based on the International Agency for Research on Cancer GLOBOCAN estimates,[1] approximately 950 000 new cases of gastric cancer were diagnosed and 700 000 deaths occurred globally. However, the incidence varies regionally and is generally higher in east Asia than in Europe and North America.[1,2]

Around 20% of advanced gastric or gastro-oesophageal junction cancers are HER2-positive.[3] In patients with these cancers, chemotherapy plus trastuzumab, a HER2-targeted monoclonal antibody, improved overall

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Research in context

Evidence before this study

We searched PubMed for clinical trials assessing treatment options for HER2-positive gastric cancer following progression on trastuzumab. The search terms used included "HER2-positive" and "gastric" and ("post-trastuzumab" or "previously treated" or "second line") with publication dates between Jan 1, 1980, and Aug 30, 2018, and filtered for English language only. We also examined relevant published congress abstracts. The published literature showed that neither trastuzumab emtansine nor lapatinib plus paclitaxel significantly improve survival compared with standard chemotherapy in patients with HER2-positive advanced gastric cancer who progressed after a previous trastuzumab regimen. Additionally, pertuzumab added to a trastuzumab regimen did not significantly improve overall survival compared with the trastuzumab regimen alone in patients with metastatic gastric cancer. PD-1 inhibitors, such as nivolumab, and TAS-102 (trifluridine or tipiracil) have shown evidence of anti-tumour activity in pretreated advanced gastric cancer. However, no HER2-targeted therapies have been approved in patients with HER2-positive disease after progression on trastuzumab-containing regimens.

Added value of this study

No standard of care is established for HER2-targeted therapy after progression on trastuzumab in HER2-positive gastric or gastro-oesophageal junction cancer. This study is the first in-human clinical study investigating trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody–drug conjugate with a topoisomerase I inhibitor payload, for the treatment of patients with advanced solid tumours, including metastatic gastric cancer previously treated with trastuzumab. 43% of patients achieved an objective response and the safety profile of trastuzumab deruxtecan was consistent with what would be expected from a HER2-targeted antibody–drug conjugate that uses a topoisomerase I inhibitor as its payload. Together, these results serve as an initial proof of concept that improved critical attributes of trastuzumab deruxtecan, such as the use of a stable linker-payload, a potential bystander effect, a short systemic half-life of the released payload, and high drug-to-antibody ratio, might translate into an improved clinical activity of HER2 antibody–drug conjugates in advanced HER2-positive gastric cancer.

Implications of all the available evidence

Trastuzumab deruxtecan showed preliminary anti-tumour activity and had a manageable safety profile in patients with gastric or gastro-oesophageal junction cancer who previously received trastuzumab. If confirmed in subsequent trials, trastuzumab deruxtecan might become a new treatment option for patients with HER2-positive gastric cancer who have previously received trastuzumab.

survival (13·8 months *vs* 11·1 months) and progression-free survival (6·7 months *vs* 5·5 months) versus chemotherapy alone in the phase 3 ToGA trial.[4] On the basis of these results, trastuzumab plus chemotherapy is the standard of care for previously untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer.[2] Newer HER2-targeted therapies, such as trastuzumab emtansine and lapatinib, did not significantly improve overall survival compared with standard chemotherapy in patients with HER2-positive advanced gastric cancer who progressed after previous gastric cancer treatment.[5,6] Additionally, pertuzumab added to a trastuzumab regimen did not significantly prolong overall survival compared with the trastuzumab regimen alone in patients with metastatic gastric or gastro-oesophageal junction cancer.[7]

These disappointing results contrast with the success of multiple HER2-targeted therapies in the treatment of HER2-positive breast cancer.[8] These findings might be in part due to the fact that gastric cancer has a higher degree of intratumoural heterogeneity in HER2 expression and amplification compared with breast cancer.[9,10] Available evidence suggests that HER2-positive gastric cancer is a heterogeneous disease with down-regulation in HER2 status post-progression on trastuzumab, as well as diverse intratumoural variations in molecular features.[11–13] Therefore, the treatment of patients with advanced HER2-positive gastric cancer previously treated with trastuzumab remains an unmet need.

Trastuzumab deruxtecan (DS-8201a) is a novel HER2-targeted antibody–drug conjugate comprised of a humanised monoclonal antibody attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload.[14] The anti-HER2 antibody is a humanised monoclonal IgG1 produced with reference to the same amino acid sequence as trastuzumab.[14] The linker is stable in plasma and selectively cleaved by lysosomal cathepsins that are upregulated in cancer cells.[14] The topoisomerase I inhibitor payload (DXd) of trastuzumab deruxtecan was ten times more potent than the active metabolite of the topoisomerase I inhibitor, irinotecan, in cell-free inhibition assays, and trastuzumab deruxtecan exhibited 99% tumor growth inhibition at a dose of 4 mg/kg in xenograft models.[14] These features, along with a high drug-to-antibody ratio of about eight, are designed for efficient delivery of the payload to tumour cells while reducing the potential systemic toxicity associated with topoisomerase I inhibitors.[14] Additionally, the cell membrane permeability of the cleaved payload enables a potent cytotoxic bystander effect, in which the released payload can diffuse across the cell membrane of targeted cells and affect cells in close proximity regardless of their HER2 expression.[15] The high drug-to-antibody ratio and the cytotoxic bystander effect can potentially allow for targeting tumours with heterogeneous HER2

expression, such as gastric cancer tumours. These unique characteristics might explain the broad anti-tumour activity of trastuzumab deruxtecan observed in preclinical studies across a wide range of tumour types with various degrees of HER2 expression.[14,15]

A phase 1, first-in-human study was started in August, 2015, with the primary objectives of selecting the recommended dose for expansion and evaluating the safety, tolerability, and activity of trastuzumab deruxtecan in advanced HER2-expressing solid tumours, including gastric cancer.[16] No dose-limiting toxicities were observed and the maximum tolerated dose was not reached during dose escalation. On the basis of preliminary safety and activity results in the dose escalation part of the study in patients with breast or gastric cancer, doses of 5·4 mg/kg and 6·4 mg/kg administered every 3 weeks intravenously were selected as the recommended doses for expansion.[16] In this Article, we report the safety and preliminary activity results from this phase 1 trial for all patients with HER2-positive gastric or gastro-oesophageal junction cancer who received trastuzumab deruxtecan at the recommended doses for expansion.

Methods

Study design and participants

We did a two-part, first-in-human, non-randomised, open-label, phase 1 study at eight hospitals and clinics in the USA and six in Japan (appendix p 3). The dose escalation part (part 1) of the study was guided by the modified continuous reassessment method and served to determine the dose-limiting toxicities and the maximum tolerated dose and to select the recommended dose for expansion.[16] Patients with advanced breast or gastric cancer in whom previous treatment had failed were enrolled in dose escalation and were treated with doses of 0·8–8·0 mg/kg of trastuzumab deruxtecan, given intravenously once every 3 weeks.[16] Detailed methods and preliminary safety and activity as well as pharmacokinetic results of the dose escalation part of the phase 1 study were previously published.[16] The dose expansion part (part 2) of the study further evaluated the safety, tolerability, and activity of trastuzumab deruxtecan at the recommended doses for expansion (5·4 mg/kg or 6·4 mg/kg every 3 weeks) in five cohorts: advanced, unresectable, or metastatic HER2-positive (immunohistochemistry 3+ or in-situ hybridisation-positive) breast cancer after trastuzumab emtansine (part 2a), HER2-positive (immunohistochemistry 3+ or immunohistochemistry 2+ and in-situ hybridisation-positive) gastric or gastro-oesophageal junction cancer post-trastuzumab (part 2b), HER2-low-expressing breast cancer (immunohistochemistry 1+ or 2+, in-situ hybridisation-negative; part 2c), other HER2-expressing (immunohistochemistry 3+, 2+, or 1+ or amplified) or HER2-mutated solid tumours (by next-generation sequencing or other methods; part 2d), and a pharmacokinetic cohort that enrolled patients with HER2-expressing advanced, unresectable, or metastatic breast cancer (immunohistochemistry 3+, 2+, 1+, or in-situ hybridisation-positive; part 2e; appendix p 4). The data in this analysis includes all patients with HER2-positive gastric or gastro-oesophageal junction cancer treated with trastuzumab deruxtecan doses of 5·4 mg/kg or 6·4 mg/kg from part 1 and part 2b. The combination of patients by cancer type from multiple cohorts was decided post hoc.

Eligible patients for part 2b were at least 18 years of age (or at least 20 years in Japan), with an Eastern Cooperative Oncology Group performance status of zero or one, measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a life expectancy of at least 3 months, and had HER2-positive (immunohistochemistry 3+ or immunohistochemistry 2+ and in-situ hybridisation-positive) gastric or gastro-oesophageal junction cancer with previous trastuzumab treatment that was refractory to standard treatment or for which standard treatment was intolerable or unavailable. Full eligibility criteria are in the appendix (pp 5–6). Tumour HER2 status was locally assessed using archival samples; new biopsy before treatment was not required.

The study protocol was approved by the independent ethics committees or institutional review boards at each site. The study was done in compliance with the protocol, and in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written, informed consent before enrolment. The full study protocol is in the appendix (pp 14–140).

See Online for appendix

Procedures

The study drug, trastuzumab deruxtecan, was supplied by the study sponsor as single-use glass vials (Daiichi Sankyo, Inc, Basking Ridge, USA; Daiichi Sankyo Co, Ltd, Tokyo, Japan). The number of treatment cycles was not fixed; 5·4 mg/kg or 6·4 mg/kg trastuzumab deruxtecan was administered intravenously to patients once every 3 weeks until withdrawal of consent, unacceptable toxicity, or progressive disease. Patients were assigned to a dose by use of a non-randomised, ad-hoc sequential block method, in which one dose was assigned for a period of time before switching to the other dose. This process was repeated, with the goal of assigning a similar number of patients to each dose. Patients remained on study until withdrawal for reasons including progressive disease, clinical progression, adverse events, withdrawal of consent, loss to follow-up, protocol violation, study termination, or other reasons at the discretion of the investigator. Dose interruptions could occur for up to 4 weeks from the planned date of study drug administration (appendix p 7). Up to two dose reductions were permitted, but doses lower than 0·8 mg/kg were not allowed (appendix pp 65–66).

Tumour assessments by CT or MRI were done every 6 weeks in the first 24 weeks following administration of the first dose, and every 12 weeks thereafter. Tumour

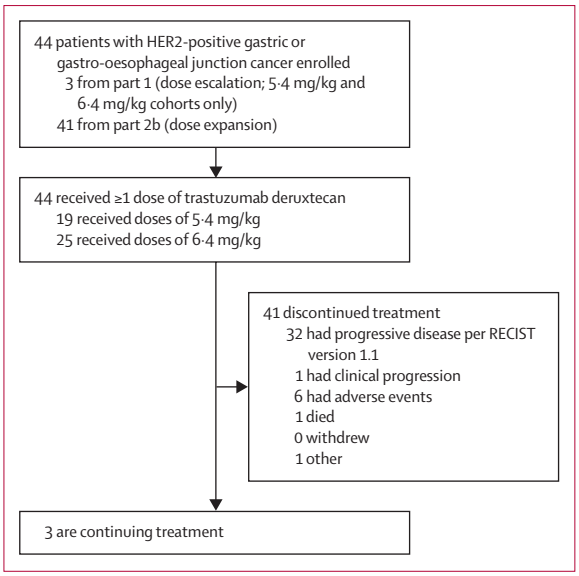

Figure 1: **Study profile**
RECIST=Response Evaluation Criteria in Solid Tumors.

response was evaluated by the investigators using RECIST version 1.1. Treatment-emergent adverse events were documented at each study visit and were graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Cardiac toxicity was monitored by left ventricular ejection fraction assessments using echocardiography or multiple gated acquisition scanning at screening, before infusion on the first day of cycles 2 and 3, and every two cycles thereafter, until the end of treatment. An independent adjudication committee was established to review reported cases of potential interstitial lung disease, pneumonitis, and organising pneumonia.

Outcomes

The primary endpoints of this study were safety and preliminary activity. Safety endpoints included treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation, serious adverse events, physical examination findings, vital sign measurements, and standard clinical laboratory parameters. Treatment-emergent adverse events of special interest included left ventricular ejection fraction decreases, QT prolongation, hepatic events, interstitial lung disease or pneumonitis, organising pneumonia, and infusion-related reactions. Adverse events were coded using Medical Dictionary for Regulatory Activities version 18.0. In this study, progressive disease was an endpoint and, consequently, was not reported as an adverse event. However, if a patient died from progressive disease with no other immediate causes, disease progression was reported as a serious adverse event.

The primary activity endpoint was the proportion of patients who achieved an objective response (complete response and partial response) as assessed by the investigators. Other activity endpoints included the proportion of patients who achieved disease control (complete response, partial response, or stable disease for

	HER2-positive gastric or gastro-oesophageal junction cancer, n=44
Age, years	68·0 (62·5–72·0)
Sex	
Male	32 (73%)
Female	12 (27%)
Country	
Japan	39 (89%)
USA	5 (11%)
Eastern Cooperative Oncology Group performance status	
0	32 (73%)
1	12 (27%)
Primary site of disease	
Gastric	36 (82%)
Gastro-oesophageal junction	8 (18%)
Differentiation grade	
Well differentiated	8 (18%)
Moderately differentiated	21 (48%)
Poorly differentiated	13 (30%)
Unknown	2 (5%)
Cancer status	
Inoperable advanced	30 (68%)
Postoperative advanced	14 (32%)
Time from initial diagnosis, months*	25·0 (17·8–37·0)
Previous lines of anticancer therapy	3·0 (2·0–5·0)
≥5 previous lines of anticancer therapy	12 (27%)
Previous trastuzumab treatment	44 (100%)
Previous irinotecan treatment	24 (55%)
Previous cancer surgery	19 (43%)
Previous radiotherapy	6 (14%)
HER2 expression (immunohistochemistry)	
3+	36 (82%)
2+	8 (18%)
In-situ hybridisation-positive	8 (18%)
In-situ hybridisation-negative or examined but not evaluated	0
Tumour size, cm	
Sum of diameters†	5·6 (3·2–11·7)
<5	22 (50%)
≥5 to <10	9 (20%)
≥10	13 (30%)

Data are median (IQR) or n (%). Baseline was defined as the last available value taken before the first dose of study drug. Safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg. RECIST=Response Evaluation Criteria in Solid Tumors. *Time from initial diagnosis was calculated as (date of first dose of study drug–date of initial diagnosis + 1) × 12 ÷ 365·25. †Median sum of diameters of target lesions per RECIST version 1.1.

Table 1: **Patient demographics and baseline characteristics (safety analysis set)**

a minimum of 5 weeks from the first dosing date), duration of response, time to response, duration of stable disease, percentage change in the sum of diameters of target lesions, progression-free survival, growth modulation index ratio, and overall survival. Progression-free survival was defined as the time from the date of the first dose to the first objective documentation of radiographic progressive disease or death due to any cause, whichever date was earlier, and overall survival was defined as the time from the date of the first dose to the date of death from any cause. Time to response was measured from the date of the first dose to the date at which criteria for complete response or partial response are first met. Duration of response was measured from the time at which complete response or partial response criteria are first met, until the first date of objectively documented progressive disease. Activity endpoints were not centrally reviewed for this analysis. A retrospective, blinded, independent review is ongoing.

Secondary endpoints were the pharmacokinetic profile of trastuzumab deruxtecan, total anti-HER2 antibody and the free payload, and the incidence of anti-drug antibody against trastuzumab deruxtecan. These secondary endpoints will be reported elsewhere.

Statistical analysis

In part 1 of the study, sample size was determined by practical considerations without any formal statistical assessments.[16] For part 2b, the planned sample size was 40 patients, which would provide at least 80% power to exclude a proportion of patients who achieve an objective response of 10% or less at the 5% type I error (one-sided), when the true proportion was 25%. The probability values for the sample size were derived based on binomial distribution using SAS (version 9.2).

In this study, the activity evaluable set included all patients in part 1 and part 2b with gastric cancer who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg, and for whom both baseline and post-treatment activity data were available. The safety analysis set included all patients with gastric cancer who received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion. An exploratory analysis of outcomes by previous irinotecan treatment was performed post hoc.

SAS (version 9.3) was used for statistical analyses. For objective response and disease control, point estimates and 95% exact binomial CIs were calculated. Time-to-event variables were summarised descriptively using the Kaplan-Meier method with confidence intervals calculated using the Brookmeyer-Crowley method. The best percentage change in the sum of the longest diameters of measurable tumours and demographic and safety data were summarised by descriptive statistics. Treatment duration in months was defined as: (the date of the last dose of study drug–the date of the first dose of study drug+21 days)×12÷365·25. Missing or dropout data were not imputed unless otherwise specified (there was no specific missing data in this study). Median progression-free survival and overall survival were calculated based on Kaplan-Meier estimates with confidence intervals computed using the Brookmeyer-Crowley method. No formal interim analyses were planned. This trial is registered at ClinicalTrials.gov, number NCT02564900, and ClinicalTrials.jp, number JapicCTI-152978.

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Haematological				
Anaemia	5 (11%)	13 (30%)	0	0
Platelet count decreased	7 (16%)	6 (14%)	2 (5%)	0
White blood cell count decreased	7 (16%)	5 (11%)	2 (5%)	0
Neutrophil count decreased	3 (7%)	7 (16%)	2 (5%)	0
Lymphocyte count decreased	0	4 (9%)	0	0
Gastrointestinal				
Nausea	30 (68%)	1 (2%)	0	0
Constipation	13 (30%)	0	0	0
Vomiting	11 (25%)	0	0	0
Diarrhoea	9 (20%)	0	0	0
Other				
Decreased appetite	27 (61%)	3 (7%)	0	0
Pyrexia	11 (25%)	0	0	0
Alopecia	8 (18%)	0	0	0
Malaise	8 (18%)	0	0	0
Fatigue	7 (16%)	0	0	0
Dysgeusia	7 (16%)	0	0	0
Hypokalaemia	1 (2%)	3 (7%)	2 (5%)	0
Hypoalbuminaemia	5 (11%)	0	0	0
Oedema	5 (11%)	0	0	0
Hyponatraemia	0	3 (7%)	0	0
Cholangitis	0	2 (5%)	0	0
Adverse events of interest				
Aspartate aminotransferase increased	3 (7%)	0	0	0
Alanine aminotransferase increased	3 (7%)	0	0	0
Blood bilirubin increased	1 (2%)	1 (2%)	0	0
Ejection fraction decreased	1 (2%)	0	0	0
Electrocardiogram QT prolonged	0	1 (2%)	0	0
Interstitial lung disease*	0	0	0	0
Organising pneumonia*	0	0	0	0
Pneumonitis*	3 (7%)	1 (2%)	0	0
Infusion-related reactions	1 (2%)	0	0	0

Data are presented as n (%). This table shows all grade 1 or 2 adverse events occurring in at least 10% of patients, grade 3–5 events occurring in two (5%) or more patients, and all adverse events of special interest regardless of incidence. The complete list of all grade 3–5 treatment-emergent adverse events is in the appendix (p 12). Patients might have more than one event per system organ class and preferred term. At each level of patient summarisation, the patient is counted once at the worst Common Terminology Criteria for Adverse Events grade. System Organ Class was coded with Medical Dictionary for Regulatory Activities version 18.0. Safety analysis set included all patients who received at least one dose of trastuzumab deruxtecan at 5.4 mg/kg or 6.4 mg/kg. *As assessed by the investigator before independent adjudication.

Table 2: **Treatment-emergent adverse events (n=44; safety analysis set)**

Role of the funding source

The study was funded by the sponsor, Daiichi Sankyo Co, Ltd, which was involved in all aspects of study design,

	Total evaluable, n=44	Previously irinotecan treated (post-hoc analysis), n=24
Median (IQR) treatment duration, months	4·4 (2·5–8·2)	3·5 (2·2–7·4)
Median (IQR) follow-up, months	5·5 (2·8–13·1)	4·6 (2·6–10·7)
Confirmed best overall response		
Complete response	0	0
Partial response	19 (43%)	10 (42%)
Stable disease	16 (36%)	9 (38%)
Progressive disease	9 (20%)	5 (21%)
Confirmed objective response, n (%; 95% CI)	19 (43·2%; 28·3–59·0)	10 (41·7%; 22·1–63·4)
Confirmed disease control, n (%; 95% CI)*	35 (79·5%; 64·7–90·2)	19 (79·2%; 57·8–92·9)
Time to response, months†		
n	21‡	12
Median (95% CI)	1·4 (1·3–1·6)	1·5 (1·2–2·6)
Duration of response, months§		
n	21‡	12
Median (95% CI)	7·0 (4·4–16·6)	6·9 (2·9–12·2)
Range	1·4–23·5¶	1·4–12·2
Progression-free survival, months		
Events	30 (68%)	18 (75%)
Median (95% CI)	5·6 (3·0–8·3)	4·1 (2·4–8·3)
Range	1·2–24·6¶	1·2–13·7

All values are n (%), unless otherwise specified. Activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg, and for whom both baseline and post-treatment activity data were available. *Disease control was calculated as the proportion of patients showing complete response, partial response, or stable disease for a minimum of 5 weeks from the first dosing date. †Time to response was measured from the date of the first dose to the date at which criteria for complete response or partial response are first met. ‡Includes two cases of unconfirmed response. §Duration of response was measured from the time at which complete response or partial response criteria are first met until the first date of objectively documented progressive disease. ¶Censored observation.

Table 3: **Anti-tumour activity outcomes (activity evaluable set)**

data collection, data analysis, and data interpretation, provided study drug, assisted in writing the report, and approved the final version of the manuscript for publication in conjunction with the authors. All authors had full access to all data in the study and provided final approval to submit the manuscript for publication.

Results

Between Aug 28, 2015, and Aug 10, 2018, 259 of 274 patients enrolled received at least one dose of trastuzumab deruxtecan at the recommended doses for expansion of 5·4 mg/kg or 6·4 mg/kg every 3 weeks (12 in the dose escalation and 247 in the dose expansion). Of these 274 patients, 44 had HER2-positive (immunohistochemistry 3+ or immunohistochemistry 2+ and in-situ hybridisation-positive) gastric or gastro-oesophageal junction cancer (three from part 1 and 41 from part 2b of the study; figure 1). Of these patients, 19 patients received the 5·4-mg/kg dose and 25 received the 6·4-mg/kg dose. Enrolment in part 2b has completed. 41 (93%) of 44 patients discontinued study treatment at the time of data cutoff (Aug 10, 2018); the most frequent reasons for discontinuation were progressive disease per RECIST (32 [73%] of 44) and adverse events (6 [14%] of 44; figure 1). The median duration of treatment was 4·4 months (IQR 2·5–8·2).

The median age of patients was 68·0 years (IQR 62·5–72·0) and the patients had a median of 3·0 (2·0–5·0) previous lines of anticancer therapies (table 1).

Safety results are presented for the 44 patients treated with at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg (table 2; appendix pp 12–13). All patients had at least one treatment-emergent adverse event of any grade, 28 (64%) patients had at least one grade 3 or worse treatment-emergent adverse event (21 [48%] were considered drug related), and 11 (25%) patients had at least one serious treatment-emergent adverse event (four [9%] were considered drug related). Decreased appetite (n=2) was the only drug-related serious treatment-emergent adverse event reported by more than one patient. Treatment-emergent adverse events leading to treatment discontinuation occurred in six (14%) patients (five [11%] were considered drug related). Drug-related treatment-emergent adverse events leading to treatment discontinuation included pneumonitis (n=3), decreased appetite (n=1), and decreased platelet count (n=1). Treatment-emergent adverse events leading to dose reduction occurred in seven (16%) patients (all of which were considered drug related). Two deaths occurred due to treatment-emergent adverse events (one due to pneumonia and one due to progression of disease); neither were considered drug-related by the investigator.

Gastrointestinal and haematological adverse events were the two most common classes of treatment-emergent adverse events (table 2). The most frequent grade 3 or worse treatment-emergent adverse events were anaemia (13 [30%] of 44 patients) and decreased platelet (eight [18%]), white blood cell (seven [16%]), and neutrophil (nine [20%]; table 2) counts.

There was one reported case of ejection fraction decrease (grade 2) and one patient experienced electrocardiogram QT prolongation (grade 3); both events were reported as recovered and patients continued receiving the study drug. Increases in alanine aminotransferase and aspartate aminotransferase each occurred in three (7%) of 44 patients (all grade 1). There was one reported case of infusion-related reactions (grade 1). Investigators reported four cases of pneumonitis (three grade 2 and one grade 3; table 2). An independent adjudication committee has assessed two cases: one was interstitial lung disease that was related to trastuzumab deruxtecan, and one was interstitial lung disease that was not related to trastuzumab deruxtecan.

All 44 patients in the HER2-positive gastric or gastro-oesophageal junction cancer group were available for the assessment of confirmed response (table 3). After a median follow-up of 5·5 months (IQR 2·8–13·1), 19 (43·2%, 95% CI 28·3–59·0) of 44 patients achieved an

objective response by investigator assessment, and 35 (79·5%, 64·7–90·2) of 44 patients achieved disease control (table 3). The median time to response was 1·4 months (95% CI 1·3–1·6) and the median duration of response was 7·0 months (4·4–16·6; table 3). The median progression-free survival was 5·6 months (3·0–8·3; figure 2) and the median overall survival was 12·8 months at data cutoff (95% CI not estimable, range 1·4–25·4 [with censoring]; appendix p 8). Six (31·6%, 95% CI 12·6–56·6) of 19 patients achieved an objective response with the 5·4-mg/kg dose, as did 13 (52·0%, 31·3–72·2) of 25 with the 6·4-mg/kg dose (appendix p 9). In a post-hoc subgroup analysis, ten (41·7%, 22·1–63·4) of 24 patients who were previously treated with irinotecan achieved an objective response and 19 (79·2%, 57·8–92·9) of 24 patients achieved disease control (table 3). Additional activity outcome data are in the appendix (pp 9–10).

Tumour shrinkage was observed in 35 [80%] of 44 patients (figure 3), all of whom had tumour shrinkage by the first 6-week postbaseline tumour assessment (appendix p 11).

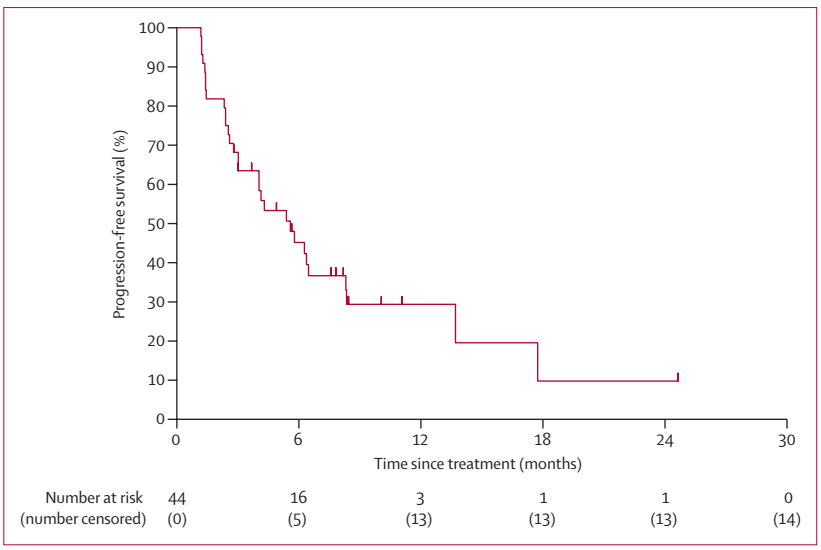

Figure 2: **Progression-free survival for trastuzumab deruxtecan 5·4 mg/kg or 6·4 mg/kg in patients with HER2-positive gastric or gastro-oesophageal junction cancer**
Progression-free survival is based on investigator assessment. Vertical tick marks indicate where data was censored.

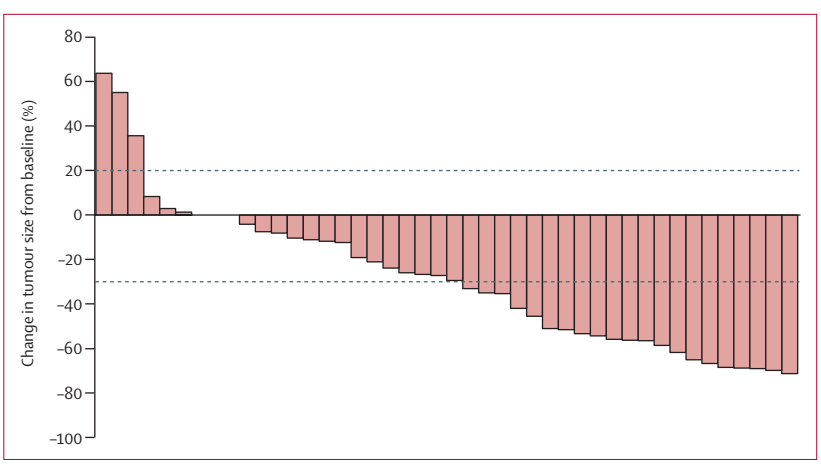

Figure 3: **Best percentage change in tumour size from baseline in individual patients with gastric or gastro-oesophageal junction cancer treated with trastuzumab deruxtecan (5·4 mg/kg or 6·4 mg/kg doses; n=44)**
Dotted lines denote 20% increase or 30% reduction in tumour size.

Discussion

This is the first in-human clinical study investigating trastuzumab deruxtecan, a HER2-targeting antibody–drug conjugate with a topoisomerase I inhibitor payload for treatment of patients with advanced solid tumours including metastatic gastric or gastro-oesophageal junction cancer previously treated with trastuzumab. In this patient population, trastuzumab deruxtecan had a manageable safety profile and showed preliminary anti-tumour activity. In a post-hoc subgroup analysis, the anti-tumour activity of trastuzumab deruxtecan was also observed in patients who previously received the topoisomerase I inhibitor, irinotecan. In addition to the findings observed in advanced gastric cancer reported here, preliminary anti-tumour activity has also been observed in patients with HER2-positive breast cancer by Tamura and colleagues,[17] as well as in non-archetype HER2-expressing tumour types (ie, non-breast or non-gastric) and in breast cancer with low expression levels of HER2.[18] In addition to trastuzumab deruxtecan, other new HER2-targeted therapies are in clinical development, such as bispecific antibodies and antibody–drug conjugates, for the treatment of HER2-positive solid tumours, including HER2-positive gastric cancer.

Metastatic HER2-positive gastric cancer that has progressed after first-line treatment with trastuzumab is often challenging to treat. In the phase 3 GATSBY study,[6] trastuzumab emtansine versus a taxane did not show significant improvements in overall survival (7·9 months *vs* 8·6 months) or progression-free survival (2·7 months *vs* 2·9 months) in patients with previously treated HER2-positive advanced gastric cancer. In the subgroup of patients with previous HER2 therapy, the overall survival also did not differ between treatment groups (8·8 months *vs* 8·9 months).[6] Similarly, in the phase 3 TyTAN study[5] of lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-positive advanced gastric cancer, there was no significant improvement in overall survival (11·0 months *vs* 8·9 months) or progression-free survival (5·4 months *vs* 4·4 months) with the addition of lapatinib to chemotherapy. In the GATSBY study,[6] the proportion of patients who achieved objective response with trastuzumab emtansine was 20·6%, and it was 27% (95% CI 19·2–34·9) in the TyTAN study[5] of lapatinib plus paclitaxel treatment. Although the sample size is smaller in our study, the confirmed proportion of patients who achieved objective response was more than 40% in

patients with heavily (including trastuzumab) pretreated advanced gastric cancer, independent of previous treatment with irinotecan. The underlying basis for this promising clinical benefit might lie in the unique characteristics of trastuzumab deruxtecan that differentiates it from other HER2-targeted therapies. These characteristics include a potent topoisomerase I inhibitor payload preferentially cleaved in tumour cells, the linker-payload stability in plasma, a potential bystander effect for the released payload, short systemic half-life of the released payload, and a high drug-to-antibody ratio of approximately eight.[14,15]

For gastric cancer, the use of a topoisomerase I inhibitor payload in trastuzumab deruxtecan might be a key attribute contributing to the preliminary anti-tumour activity observed. Treatment with topoisomerase I inhibitors, such as irinotecan, significantly improves overall survival in patients with metastatic gastric cancer who have progressed after a first-line treatment regimen compared with best supportive care and is recommended as second-line therapy in these patients.[2,19,20] In this study, the lack of cross-resistance between irinotecan and trastuzumab deruxtecan could potentially be due to a more efficient drug delivery of the payload with trastuzumab deruxtecan resulting in a higher concentration of the cytotoxic agent in the tumour environment compared with the cytotoxic agent alone. However, further research is needed to establish the reason for the apparent lack of cross-resistance.

Preclinical in-vitro and in-vivo studies suggest that trastuzumab deruxtecan has a potent cytotoxic bystander effect, by contrast with trastuzumab emtansine.[15] This bystander effect might be particularly important in tumours with high heterogeneity in HER2 expression, such as gastric cancer. The cytotoxic bystander effect with trastuzumab deruxtecan might enable the payload to affect neighbouring tumour cells regardless of HER2 expression because the released free payload can diffuse across the cell membrane of targeted cells. By some estimates, less than 10% of gastric cancers show HER2 expression in more than 5% of tumour cells.[21] Therefore, the ability to affect neighbouring non-HER2-expressing tumour cells might be useful in the treatment of HER2-positive gastric cancer. The observed bystander effect with trastuzumab deruxtecan is enabled by the cell membrane permeability of the released DXd payload. The linker for trastuzumab deruxtecan was designed to be cleaved by lysosomal enzymes, such as cathepsins B and L, which are upregulated in tumour cells. Trastuzumab deruxtecan has a self-immolative moiety between the tetrapeptide linker and the payload, which is rapidly hydrolysed, resulting in the release of DXd. Trastuzumab emtansine has a non-cleavable linker attached to a tubulin inhibitor payload, which together comprise the biologically active linker-payload component (Lys-SMCC-DM1).[15] DXd has a higher cell membrane permeability than Lys-SMCC-DM1 (permeability coefficient in parallel artificial membrane permeability assay of 12·2 *vs* <0·1 at pH 7·4).[15] However, the potential link between bystander effect and the anti-tumour activity of trastuzumab deruxtecan in humans needs further translational research.

The safety profile of trastuzumab deruxtecan was consistent with what would be expected for a HER2-targeted antibody–drug conjugate that uses a topoisomerase I inhibitor as its payload. Most common classes of treatment-emergent adverse events were gastrointestinal and haematological in nature. In breast cancer, cardiotoxicity is a serious side effect of treatment with HER2-targeted therapies, including trastuzumab.[22–24] In the ToGA trial,[4] the addition of trastuzumab to chemotherapy did not increase cardiotoxic side-effects associated with standard fluoropyrimidine-based and platinum-based chemotherapy regimens in patients with gastric cancer. In our study, the incidence of left ejection fraction decrease associated with trastuzumab deruxtecan in gastric cancer patients was low. This was also true for the overall study population, including those cohorts with longer duration of treatment than the gastric cancer cohort. However, because it is an important potential class effect, the cardiac safety profile of trastuzumab deruxtecan will continue to be further characterised in the ongoing studies. Additionally, the safety and tolerability of the combination of trastuzumab deruxtecan with other anticancer regimens is being assessed in ongoing and planned phase 1 trials.

Treatment-induced pulmonary toxicities including interstitial lung disease have been reported as rare, potentially life-threatening adverse events associated with trastuzumab and trastuzumab emtansine, as well as with irinotecan.[25–27] Drug-related interstitial lung disease, pneumonitis, or organising pneumonia, including five fatal cases, have been reported in our study in the overall study population.[18] Because this is a potentially serious risk with trastuzumab deruxtecan, a robust monitoring and management plan has been established and implemented across all studies of trastuzumab deruxtecan with regards to interstitial lung disease, pneumonitis, or organising pneumonia. The management plan for interstitial lung disease, pneumonitis, or organising pneumonia is guided by the most recent statement for the diagnosis and treatment of drug-induced lung injuries by the Japanese Respiratory Society.[28] When interstitial lung disease, pneumonitis, or organising pneumonia is suspected, early diagnosis through appropriate imaging, laboratory tests, and pulmonary consultation as well as withdrawal of study medication and management with steroids for moderate to severe cases are recommended. Further research is ongoing (including independent adjudication of all suspected events) to better characterise these events, to understand the risk factors, and to further optimise management of interstitial lung disease, pneumonitis, or organising pneumonia associated with trastuzumab deruxtecan treatment.

This study had some limitations that might affect the generalisation of the results. This was a non-randomised, phase 1 study with a heterogeneous patient population and a relatively small sample size. Additionally, HER2 immunohistochemistry status was locally assessed using archival samples, which is of importance because loss of HER2 overexpression has been previously reported following progression on trastuzumab.[13,29] HER2 status, confirmed by centralised testing, needs to be further assessed in future studies of trastuzumab deruxtecan. Another limitation is that the reported results are based on local radiology review; however, a retrospective, blinded, independent review is ongoing. Finally, the generalisation of the results might be reduced by the fact that most patients were from Japan and the primary site of disease was gastric as opposed to gastro-oesophageal junction.

In this phase 1 study, trastuzumab deruxtecan showed preliminary anti-tumour activity and a manageable safety profile in patients with advanced HER2-positive gastric cancer, including those who previously received irinotecan. Preliminary results from this trial led to trastuzumab deruxtecan receiving SAKIGAKE Designation (an expedited review programme) for the treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer by the Japan Ministry of Health, Labour and Welfare. The ongoing DESTINY-Gastric01 study, a randomised, multicentre, open-label, phase 2 study, will assess the efficacy and safety of trastuzumab deruxtecan versus physician's choice of treatment in 220 patients with HER2-expressing gastric or gastro-oesophageal junction cancer who progressed after two or more previous regimens and previously received trastuzumab (NCT03329690). In addition to the primary cohort (patients with HER2-positive gastric cancer who progressed after two or more regimens and previously received trastuzumab), DESTINY-Gastric01 also includes exploratory cohorts assessing HER2-low gastric cancer (immunohistochemistry 1+ or immunohistochemistry 2+ and in-situ hybridisation-negative) treatment-naive to HER2-targeted therapies. Several other ongoing studies are investigating the efficacy and safety of trastuzumab deruxtecan in different HER2-expressing solid tumour types, including HER2-positive breast cancer, as monotherapy or in combination with other agents. In breast cancer, the ongoing pivotal phase 2 DESTINY-Breast01 trial (NCT03248492) is assessing the efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab emtansine. Two phase 3 trials in HER2-positive breast cancer (DESTINY-Breast02 [NCT03523585] and DESTINY-Breast03 [NCT03529110]) are also ongoing. These studies will further expand our understanding of trastuzumab deruxtecan efficacy and safety in various settings. If the results in gastric cancer are confirmed in subsequent trials, trastuzumab deruxtecan might become a new treatment option for patients with HER2-positive gastric cancer who have previously received trastuzumab.

Contributors

All authors were involved in the conception or design of the study and in drafting and revising the manuscript for publication. KS, HI, ST, KT, HP, SM, JT, SK, KY, SI, and TD were involved with data collection. KS, YF, MS, and JS were involved in analysing data. All authors were involved in the interpretation of data and approved the final version of the manuscript.

Declaration of interests

KS reports consulting or advisory roles for Astellas, Lilly, Bristol-Myers Squibb, Takeda, Pfizer, and Ono, personal fees from Novartis, AbbVie, and Yakult, and research funding from Lilly, Ono, Sumoitomo Dainippon, Daiichi Sankyo, Taiho, Chugai, and Merck Sharp & Dohme Corporation (MSD). HI received grants and personal fees from Daiichi Sankyo during the conduct of this study and, outside the submitted work, grants from Chugai, Pfizer, AstraZeneca, MSD, Kyowa Hako Kirin, GlaxoSmithKline, Lilly, Novartis, and Bayer, and personal fees from Chugai, Eisai, Pfizer, and AstraZeneca. ST reports grants from Daiichi Sankyo during the conduct of the study, personal fees from Novartis, MSD, Eisai, Taiho, Chugai, Daiichi-Sankyo, Bayer, and AstraZeneca, and grants from MSD, Eisai, Taiho, Chugai, Daiichi Sankyo, Bayer, AstraZeneca, and Quintiles outside the submitted work. KT reports research funding from Daiichi Sankyo paid to his institution during the conduct of the study. HP reports non-financial support from Daiichi Sankyo. SM reports personal and other fees from Daiichi Sankyo and Seattle Genetics, personal fees from Carrick and Puma, and other fees from Novartis. JT received preclinical research funds from Daiichi Sankyo during the conduct of this study and outside the submitted work, honorarium from Novartis, Taiho, Eisai, Chugai, and Kyowa Hakko Kirin, personal fees for participating in advisory boards for Eisai and Asahi Kasei, and support for travel expenses from Daiichi Sankyo. SK reports grants from Eli Lilly Japan KK, Taiho, Boehringer Ingelheim, Ono, and Bristol-Myers Squibb KK. KY reports grants and personal fees from Daiichi Sankyo, Ono, Taiho, Yakult Honsha Co, and Lilly, personal fees from Bristol-Myers Squibb, Merck, Takeda, Bayer, and Sanofi, and grants from MSD and Dainippon Sumitomo. SI reports grants and personal fees from Lilly, personal fees from Taiho, and grants from Bristol-Myers Squibb, Chugai Pharma, Daiichi Sankyo, Lilly, Merck Serono, and Novartis. KS, YF, MS, and JS are full-time employees of Daiichi Sankyo. TD received grants from Daiichi Sankyo during the conduct of this study and, outside the submitted work, grants from Lilly, Chugai, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Taiho, Novartis, Merck Serono, Astellas, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Sumitomo Group, Celgene, Bristol-Myer Squibb, AbbVie, and Quintiles and personal fees from Lilly, Chugai, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, and Amgen.

Data sharing

De-identified individual participant data and applicable supporting clinical trial documents may be available upon request at the Vivli website. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc, will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at Vivli's Daiichi Sankyo web page. For more information, see appendix p 2.

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